

Claims

1. A method for preparing optionally substituted {N-[1-(S)-carbalkoxy-3-phenylpropyl]-S-alanyl-2S, 3aR, 7aS-octahydroindole-2-carboxylic acid} and pharmaceutically acceptable salts thereof, characterized in that a racemic mixture of optionally substituted *trans*-octahydroindole-2-carboxylic acid is reacted with the N-carboxyanhydride of {N-[1-(S)-alkoxycarbonyl-3-phenylpropyl]-L-alanine}, which is optionally substituted on the phenyl ring, in a suitable inert solvent, and subsequently the resulting optionally substituted {N-[1-S-carbalkoxy-3-phenylpropyl]-S-alanyl-2S, 3aR, 7aS-octahydroindole-2-carboxylic acid} is isolated.
- 15 2. The method as claimed in claim 1, characterized in that the compound is isolated by crystallization.
- 20 3. The method as claimed in claim 1 or 2, characterized in that the compound {N-[1-S-carbethoxy-3-phenylpropyl]-S-alanyl-2S, 3aR, 7aS-octahydroindole-2-carboxylic acid} (trandolapril) is prepared.
- 25 4. The method as claimed in either of claims 2 or 3, characterized in that the resulting diastereomer mixture is converted into a suitable salt, preferably the hydrochloride, sulfate or phosphate, preferably into the hydrochloride, the desired diastereomer salt is crystallized and then the desired compound, preferably, 30 for example, trandolapril, is liberated therefrom, and the compound obtained in this way is subsequently converted where appropriate into a suitable salt.

5. The method as claimed in either of claims 2 or 3, characterized in that desired diastereomer, preferably trandolapril, is crystallized directly from the reaction
5 mixture and, where appropriate, the compound is subsequently converted into a suitable salt.

6. The method as claimed in any of claims 1-5, characterized in that optionally substituted [N-(1-S-
10 carbalkoxy-3-phenylpropyl)-S-alanyl-2S, 3aR, 7aS-octahydroindole-2-carboxylic acid] compounds in which "carbalkoxy" means carbethoxy, carbopropoxy or carbobutoxy, preferably carbethoxy, and the 3-phenylpropyl radical is optionally substituted on the phenyl by methyl,
15 ethyl, propyl or butyl, preferably in the ortho or para position, and is preferably unsubstituted, are prepared.

7. The method as claimed in any of claims 1-6, characterized in that a pharmaceutically acceptable salt
20 is prepared, preferably a salt with hydrochloric acid, oxalic acid, tartaric acid, methylsulfonic acid, benzenesulfonic acid.

8. The method as claimed in any of claims 1-7,
25 characterized in that the reaction of the NCA of {N-[1-(S)-alkoxycarbonyl-3-phenylpropyl]-L-alanine} with *rac*. octahydroindole-2-carboxylic acid is carried out at a temperature in the range from about -20°C to room temperature, preferably in the range from about -20°C to
30 0°C, with the NCA of {N-[1-(S)-alkoxycarbonyl-3-phenylpropyl]-L-alanine} preferably being added to a suspension of *rac*. *trans*-octahydroindole-2-carboxylic acid in a mixed aqueous solvent system.

9. The method as claimed in claim 8, characterized in that the molar ratio of the NCA to *rac.* *trans*-octahydroindole-2-carboxylic acid is in the range from 1:1 to 1:1.6,
5 preferably about 1:1.3, and the acid value (pH) is kept in the basic range, preferably in the range from pH 9 to pH 10, during the reaction.

10. The method as claimed in claim 8, characterized in
10 that mixtures of water and of a water-miscible organic solvent, preferably acetone, dioxane or tetrahydrofuran, preferably acetone, is used as mixed aqueous solvent system.

15 11. The method as claimed in any of claims 1-10, characterized in that the crystallization is carried out at a temperature in the range from -5°C to +30°C, the water content of the organic solvent during the crystallization of the salt being in the range of 2-4% by
20 weight, preferably of 2.5-3.5% by weight and preferably of about 3% by weight, and the water content of the organic solvent during the crystallization of diastereomer A1 being in the range of 0.05-4.0% by weight, preferably in the range of 1.5-3.0% by weight.

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12. The method as claimed in claim 11, characterized in that an organic ester, preferably methyl acetate, ethyl acetate, propyl acetate, preferably ethyl acetate, is used as organic solvent.

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13. The method as claimed in any of claims 1-12, characterized in that the product obtained by crystallization is purified by recrystallization or by

elutriation in an organic solvent or in a mixture of such a solvent with water, preferably in acetone/water, acetone, acetone/MTBE, ethyl acetate or ethyl acetate/MTBE.

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14. The crystalline polymorphic, substantially anhydrous, form A of trandolapril characterized by the XRD data listed in table 2.

10 15. The crystalline polymorphic hydrous form B of trandolapril characterized by the XRD data listed in table 5 and by the fact that this form B has a water content in the range of 4-4.4% by weight.

15 16. A method for preparing polymorphic form A as claimed in claim 14, characterized in that trandolapril is crystallized from an organic solvent or a mixture of organic solvents, preferably acetone/cyclohexane.

20 17. The method as claimed in claim 16, characterized in that the water content of the solvent does not exceed 0.2% by weight (<0.2% by weight).

25 18. A method for preparing polymorphic form B as claimed in claim 15, characterized in that trandolapril is crystallized from water or mixed aqueous systems at 0-25°C, preferably from methanol/water or acetone/water mixtures at 0-25°C.

30 19. The use of form A as claimed in claim 14 and of form B as claimed in claim 15 as therapeutic active ingredients, preferably for treating cardiovascular

diseases, preferably for treating high blood pressure and heart failure.